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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,054	03/19/2004	Juha Punnonen	0156.160US	7977

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,054	PUNNONEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-96* is/are pending in the application.

4a) Of the above claim(s) *80-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-10-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 51-79 and elect species CTLA-4, in the reply filed on 8-10-06 is acknowledged. The traversal is on the ground(s) that applicants request examiner to consider the subject matter of the claims of Application No. 10/223,507 in view of the pending claims in the instant application. This is not found persuasive because of the reasons set forth in the preceding Official action mailed 7-10-06. Examiner is confused why and what to consider regarding the subject matter of the claims in Application No. 10/223,507. Examiner will consider the subject matter of the elected claims and species of the instant invention but not the subject matter of other patent application.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 80-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8-10-06.

Applicants' preliminary amendment filed 11-8-04 has been entered. Claims 1-50 have been canceled. Claims 51-96 have been added. Claims 51-96 are pending. Claims 51-79 and the elected species CTLA-4 are considered.

Double Patenting

3. Applicant is advised that should claim 54 be found allowable, claims 63 and 70 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

4. Applicant is advised that should claim 57 be found allowable, claim 64 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

5. Applicant is advised that should claim 58 be found allowable, claim 65 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

6. Applicant is advised that should claim 59 be found allowable, claim 66 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

7. Applicant is advised that should claim 60 be found allowable, claim 67 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

8. Applicant is advised that should claim 62 be found allowable, claim 69 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

9. Applicant is advised that should claim 61 be found allowable, claim 71 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 57, 59, 64, 66, 75, 76 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "CTLA-4" in claims 57, 64, 75 and 76 is vague and renders the claim indefinite. The term "CTLA-4" is an abbreviation which can stand for different meanings. It is unclear what meaning is intended. Spelling out the term "CTLA-4" would be remedial.

The term "ICAM-1" in claims 57, 64, 75 and 76 is vague and renders the claim indefinite. The term "ICAM-1" is an abbreviation which can stand for different meanings. It is unclear what meaning is intended. Spelling out the term "ICAM-1" would be remedial.

The phrase "said enterotoxin receptor binding domain is obtained from a cholerae enterotoxin ... **and** campylobacter toxin" in claim 59, 66 and 78 is vague and renders the claim indefinite. It is unclear whether the binding domain is obtained from any one of the listed enterotoxin, combination of two or more enterotoxin, or all of the listed enterotoxin. If the binding domain is obtained from more than one enterotoxin, it is unclear how the binding domains are arranged, as independent binding domain or as a fusion protein with various order of arrangement.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 51-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

14. Claims 51-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a binding moiety for use with a genetic vaccine as disclosed by Stemmer et al., Ledley et al and Patten et al., set forth below, does not reasonably

provide enablement for the claimed method for producing a binding moiety in vitro or in vivo as discussed below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 51-70 are drawn to a method for producing a binding moiety for use with a genetic vaccine by creating a library of recombinant polynucleotides from a plurality of parental polynucleotides, wherein said parental polynucleotides differ from each other by at least two nucleotides, said recombinant polynucleotides containing a region encoding a polypeptide comprising a nucleic acid binding domain, transfecting a population of host cells with a library of genetic vaccine vectors comprising said recombinant polynucleotide and a binding site for the encoded polypeptide, the polypeptide is expressed and bind to the vector binding site to produce vector-binding moiety complex, lysing the host cells, contacting the vector-binding moiety complex with a target cell, and isolating the recombinant polynucleotide from the target cell to produce a population of selected polynucleotide. Claim 52, 61 and 68 specify the vectors further comprise a selection marker. Claims 54, 63 and 70 specify the method is applied reiteratively to said selected polynucleotide. Claims 55-60 and 64-67 specify the recombinant polynucleotide further comprises a ligand, such as CTLA-4 or enterotoxin receptor binding domain, or a cell-specific ligand. Claims 71-79 are similar to claims 51-70 except the recombinant polynucleotide in claim 71 comprises a region encoding a polypeptide comprising a nucleic acid binding domain and a region encoding a ligand that binds to the surface of a cell of interest.

The specification only discloses prophetic examples for selection of bacteriophage-derived delivery vehicles having enhanced ability to enter target cells and animal models for

screening genetic vaccine vector. The claims encompass expressing polynucleotides encoding nucleic acid binding domains alone or expressing the binding domain and a ligand, such as CTLA-4, enterotoxin or cell-specific ligand, to form a vector binding moiety complex, transfecting target cells with said vector-binding complex moiety complex and isolating recombinant polynucleotide to produce a population of selected polynucleotides *in vitro* or *in vivo*.

Claims 51-54, 63 and 70 read on expressing a polypeptide comprising a nucleic acid binding domain, binding of said polypeptide to a binding site for said polypeptide to form vector-binding moiety complex, and contacting said complex with a target cell of interest. The specification fails to provide adequate guidance and evidence for how the vector-binding moiety complex can be up taken by the target cell of interest just by contacting said target cell. The vector-binding moiety complex only contains a polypeptide binding to a polynucleotide comprising nucleic acid binding site of said polypeptide. There is no ligand or cell-specific ligand expressed or complexed with said vector-binding moiety complex. It is unclear how the vector-binding moiety complex would be up taken by the target cell of interest in vitro or in vivo.

The specification fails to provide adequate guidance and evidence for how the polynucleotide encoding a nucleic acid binding domain is associated with the polynucleotide encoding a ligand or a cell-specific ligand in the library of recombinant polynucleotides. It is unclear whether those two polynucleotides are fused together or they are on separate vectors? If they are in the same polynucleotide molecule, it is unclear whether the nucleic acid binding domain and the ligand are expressed as independent polypeptide or as a fusion protein. The specification also fails to provide adequate guidance and evidence for how the expression

products of those two polynucleotides would form a recombinant binding-moiety and how to use said recombinant binding moiety to bind to a vector to form a vector-binding moiety complex that can be up taken by a target cell of interest *in vitro* and *in vivo*. The specification fails to provide enabling disclosure for how the vector-binding moiety complex would get into the target cell for isolating the desired selected polynucleotides when the expressed nucleic acid binding domain and the ligand are expressed separately and are not associated with each other. A dissociated ligand that is separate from the nucleic acid binding domain can not deliver vector having the binding site for nucleic acid binding domain to target cells *in vitro* or *in vivo*. Thus, one skilled in the art at the time of the invention would not know how to use the claimed method to produce a population of selected polynucleotides *in vitro* and *in vivo*.

The claims read on gene transfer *in vivo* and recovery of expressed gene product *in vivo*. The specification fails to provide adequate guidance and evidence for how to transfect a population of host cells with a library of genetic vaccine vector comprising a polynucleotide encoding a nucleic acid binding domain or polynucleotides encoding said binding domain and a ligand to produce a vector-binding moiety complex in vivo and contacting said vector-binding moiety complex with a target cell in vivo to isolate a population of selected polynucleotides. The biological environment *in vivo* is very different from the biological environment *in vitro*. The factors in *in vitro* environment were well controlled, such as the type of medium, the ingredients of the medium, the temperature of the medium and the type of the container used. However, there are various unknown bioactive factors that can not be controlled *in vivo* and these bioactive factors interact with each other and with various regulatory elements. It was known in the art that a gene which is expressed *in vitro* is not necessarily to be expressed *in vivo*

in various cell types because the microenvironment *in vitro* is different from the microenvironment *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. Verma et al., 1997 (Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, right column).

Administration route plays a very important role in determining whether sufficient protein of interest can be expressed and present at the target cells in vivo. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). Further, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). Administration routes and type of target cells

for gene expression affect the expression of the nucleic acid binding domain and ligand when a population of host cells are transfected with a library of genetic vaccine vector *in vivo* and when a vector-binding moiety complex is contacted with a target cell of interest *in vivo*. Absent specific guidance one skilled in the art at the time of the invention would not know how to transfect a population of host cells with a library of genetic vaccine vector to express a polypeptide containing a nucleic acid binding domain and a ligand in vivo and to contact a vector-binding moiety complex with a target cell of interest so as to produce a population of selected polynucleotide in vivo.

For the reasons discussed above, one skilled in the art at the time of the invention would have to engaged in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, the level of skill which is high, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 51-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. 1997 (WO 97/20078) in view of Ledley et al., 1994 (WO 94/25608) and Patten et al., 1997 (Current Opinion in Biotechnology, 8: 724-733).

Claims 51-70 are drawn to a method for producing a binding moiety for use with a genetic vaccine by creating a library of recombinant polynucleotides from a plurality of parental polynucleotides, wherein said parental polynucleotides differ from each other by at least two nucleotides, said recombinant polynucleotides containing a region encoding a polypeptide comprising a nucleic acid binding domain, transfecting a population of host cells with a library of genetic vaccine vectors comprising said recombinant polynucleotide and a binding site for the encoded polypeptide, the polypeptide is expressed and bind to the vector binding site to produce vector-binding moiety complex, lysing the host cells, contacting the vector-binding moiety complex with a target cell, and isolating the recombinant polynucleotide from the target cell to produce a population of selected polynucleotide. Claim 52, 61 and 68 specify the vectors further comprise a selection marker. Claims 53, 69 and 72 specify the target cells are muscle cells, monocytes, B cells, and dendritic cells etc. Claims 57, 64, 75 and 76 specify the ligand is CD2, CD28, CTLA-4, CD40, CD40 ligand, ICAM-1, or Fc portion of Ig G etc. Claims 54, 63 and 70 specify the method is applied reiteratively to said selected polynucleotide. Claims 55-60 and 64-

67 specify the recombinant polynucleotide further comprises a ligand, such as CTLA-4 or enterotoxin receptor binding domain, or a cell-specific ligand. Claims 71-79 are similar to claims 51-70 except the recombinant polynucleotide in claim 71 comprises a region encoding a polypeptide comprising a nucleic acid binding domain and a region encoding a ligand that binds to the surface of a cell of interest.

Stemmer teaches a method for the production of nucleic acid fragments or polynucleotides encoding mutant proteins by repeated cycles of mutagenesis, shuffling and selection of nucleic acids to generate polynucleotides having desired characteristic by iterative selection and recombination for the molecular evolution *in vitro* or *in vivo* of proteins (e.g. abstract). Stemmer teaches a method of evolving a polynucleotide sequence toward a desired property comprising recombining at least a first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence, screening at least a first recombinant sequence from said library, recombining said first recombinant sequence with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library, and screening at least one further recombinant polynucleotide from said further library (e.g. p.164).

Stemmer does not teach generating a library of recombinant nucleic acid encoding a polypeptide comprising a nucleic acid binding domain and/or a ligand which binds to the surface of a target cell, or a cell-specific ligand.

Ledley teaches generating a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA, such as histone or transacting regulatory element, and a complex for efficient gene

transfer comprising a DNA molecule specifically and non-specifically bound to the chimeric recombinant DNA-binding protein (e.g. p. 26, 27, abstract). Ledley also teaches the ligands for specific or nonspecific receptors on the cell surface can be immunoglobulins, T-cell receptors, cell surface markers from lymphocytes, bacterial proteins, cell adhesion molecules, and viral proteins etc., (e.g. p. 15).

Patten teaches "viral vaccine vectors can be enhanced by DNA shuffling to give desired properties of tropism, stability and expression level", and DNA shuffling could be a tool " for increasing the efficiency and success rate of the development of novel whole organism, viral, bacterial and recombinant protein vaccines" (e.g. p. 732).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the first and second forms of polynucleotide sequences taught by Stemmer with polynucleotide sequences encoding a DNA-binding element and a ligand binding to a receptor on a target cell as taught by Ledley for the production of a genetic vaccine as taught by Patten.

One having ordinary skill at the time of the invention would have been motivated to do so because the generation of a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA could facilitate the efficiency of gene transfer and the effects of a genetic vaccine to stimulate immune response in a host.

It is noted that the cited references Stemmer, Ledley, and Patten have been provided in the parent Application No. 09/247,886. Therefore, these references will not be provided in the instant Official action.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
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